(28)

No. 03-1237

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IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

REPLY BRIEF FOR PETITIONER

DONALD R. DUNNER
THOMAS H. JENKINS
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

E. JOSHUA ROSENKRANZ
Counsel of Record
M. PATRICIA THAYER
JAMES N. CZABAN
GINA M. PARLOVECCHIO
NISHITA DOSHI
HELLER EHRMAN LLP
Times Square Tower
7 Times Square
New York, NY 10036
(212) 832-8300

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REPLY BRIEF FOR PETITIONER

INTRODUCTION

Everyone agrees on the answer to the question presented: Preclinical experiments reasonably related to an IND application *are* as immune from patent infringement claims as clinical trials. With this concession, Integra pulls the lone prop out from under the judgment below. This case now revolves around Integra's alternative ground for supporting the judgment: that the evidence was sufficient, in any event, to exclude each of the Scripps experiments from the FDA exemption's protection. This alternative ground rests on legal premises that are every bit as flawed as the Court of Appeals' rationale—and equally destructive of the FDA exemption's core purpose, to speed promising drugs to market after patent expiration. In the interest of providing guidance to the lower courts, drug innovators, researchers, and patent holders, the Court should address these premises, reject them, and reverse outright.

On the temporal question—whether the research had progressed to the point where, as a matter of law, a drug innovator could reasonably believe that the FDA was an appropriate audience for the ensuing research—Integra concedes the most important point: Merck reasonably believed it had a viable cure for cancer when it commissioned all the experiments in question. Nevertheless, Integra suggests that a drug innovator cannot invoke the exemption until it has settled upon the optimum structure of the drug and has definitively decided to invest all of the millions of dollars necessary to secure FDA approval. This position finds no support in the statutory language or core purposes of the FDA exemption. Since the tweaking to optimize structure is an essential part of the preclinical process, Integra's position would have the same practical

impact as a holding that the FDA exemption does not cover preclinical studies at all.

So, too, would Integra's position on the substantive prong of the FDA exemption, focusing on what sorts of information are relevant to the FDA. Integra argues that a reasonable jury could have believed one witness' testimony that the FDA would have no interest in the information Scripps produced, either because an IND application is about only safety or because experiments performed under non-GLP conditions are irrelevant. The FDA itself has entered this case to explain that Integra's witness misrepresented the law; IND applications invariably present data beyond safety, from experiments performed under non-GLP conditions. If any patent owner could defeat the FDA exemption by calling a witness to misstate the law, then, again, the exemption is of little value.

Integra's final argument is that the Scripps research had the additional purpose of advancing the basic understanding of diseases—which, again, is common—and that *some* experiments (only 11% of them) compared the lead drug candidate with other non-infringing structures to ensure that Merck would proceed to the FDA with the safest and most effective drug candidate. The FDA exemption, however, asks only whether a "use"—in this case, an experiment—is justified, not whether the researcher or sponsor has other subjective *purposes* or whether the *information* can be used in other ways. Moreover, any experiment comparing a lead drug candidate to analogs is reasonably related to the development of information for the FDA as a matter of law.

Numerous amici wrangle over whether, and under what circumstances, research tools lose the protection of the FDA exemption, but this important question must await another day. Integra has never argued that the Scripps experiments would have fallen outside the scope of the FDA exemption

simply because the infringing RGD peptides were being used as research tools, and, in fact, they were not.

Finally, Integra's various claims of procedural bar fail. Merck did challenge the sufficiency of the evidence before the Court of Appeals, explicitly and at length, just as it did before the District Court, and has never wavered from its theory of the case before this Court.

ARGUMENT

I. THE FDA EXEMPTION COVERS THE ACCUSED EXPERIMENTS AS A MATTER OF LAW.

A. Integra Concedes That The FDA Exemption Covers Research That Is Submitted To The FDA In Connection With An Investigational New Drug Application.

There is no disagreement about the answer to the question presented: "Does th[e] FDA safe harbor protect the [preclinical] animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials with humans?" Merck's answer is yes. Integra agrees. Resp. at 27.[1] So does the Government. U.S. Br. at 8-15. Not one of the 18 other amici disagrees.

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[1] All abbreviations adopted in Merck's opening brief will apply to this brief. Beyond that, the Brief for Petitioner will be cited as "Pet. Br."; Respondents' Brief on the Merits will be cited as "Resp."; and Merck's opening brief and reply brief in the Court of Appeals will be cited as "Merck CA Br." and "Merck CA Rep.," respectively. Merck's certiorari petition and reply will be cited as "Pet'n" and "Pet'n Rep.," respectively; and Integra's Brief in Opposition to certiorari will be cited as "Cert. Opp." The Government's amicus brief will be cited as "U.S. Br.," and other amicus briefs will be cited as "___ Br.," according to the name or abbreviation of the lead amicus.

The Court of Appeals stands alone in the view that the FDA exemption protects the *clinical* phase but not the *preclinical*. "[I]f the Federal Circuit opinion actually means what Merck and the government say it means, Integra does not defend it." Resp. at 27.

Not only is that what the opinion means, but the preclinical/clinical distinction is the linchpin of the Court of Appeals' ruling. *See* U.S. Br. at 8-9. The Court of Appeals framed the question in those terms: "This court has not considered the question arising in this case, namely, whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability . . . ." P.A. 10a (emphasis added). The court held that the answer was no, because: "In this case, the Scripps work sponsored by Merck *was not clinical testing to supply information to the FDA* . . . ." P.A. 12a (emphasis added). And the court concluded: "Thus, the Scripps work sponsored by Merck was not 'solely for uses reasonably related' to *clinical testing* for FDA." *Id.* (emphasis added).

Because no one is prepared to defend the Court of Appeals' rationale, Resp. at 27, this Court could reverse the judgment and, without further guidance, direct the Court of Appeals to resolve the JMOL motion on the proper legal standard. *See Boyle v. United Tech. Corp.*, 487 U.S. 500, 514 (1988). But in the interest of providing guidance to the lower courts and to drug innovators, researchers, and patent holders, the Court should address the alternative ground that Integra raised in its opposition to certiorari and reiterates in its merits brief. The alternative ground merits this Court's attention because it depends on erroneous legal theories that, if accepted, would gut the FDA exemption for new drugs every bit as much as the Court of Appeals' rationale. *See Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 230 (1993). These approaches should be

rejected, and this Court should reverse the Court of Appeals outright.

The only outcome that is inconceivable from the current posture is the one Integra advocates. In a passage reminiscent of the rules of croquet in Wonderland, Integra contends it can concede error as to the crux of the Court of Appeals' judgment, declare that "there is essentially no controversy for this Court to adjudicate," and nevertheless demand that "[t]his Court should *affirm* the Federal Circuit's judgment" outright, without this Court, or any other, ever assessing Integra's alternative ground. Resp. at 2 (emphasis added); *see id.* at 23, 28. Integra erects this position from cases that stand for the proposition that a petitioner who *loses* on the question presented cannot foray beyond the certiorari petition and offer an alternative basis on which to prevail. *See* Resp. at 21. Neither these cases nor any other support the proposition that Merck, upon *prevailing* on the question presented, is forever barred from fending off *Integra*'s alternative theory for nevertheless *upholding* the judgment, just because Merck did not present Integra's arguments in its own certiorari petition. *See Bennett v. Spear*, 520 U.S. 154, 166-67 (1997) (addressing respondent's alternative grounds for affirmance when respondent does not defend Court of Appeals' rationale).

B. The Statutory Language Of The FDA Exemption Dictates Its Scope.

Neither Integra nor any amicus takes issue with the proposition that the FDA exemption entails two inquiries, one temporal and the other substantive. *See* Pet. Br. at 44; U.S. Br. at 16. The temporal inquiry focuses on how far along the trajectory of drug development an innovator must progress before it can avail itself of the exemption as a matter of law. The substantive inquiry focuses on what categories of information are indisputably relevant to the

FDA's regulatory role. Beyond that, several amici debate about the possibility of a third prong, not at issue here and never pressed by Integra: whether patented research tools fall outside the FDA exemption, categorically or under certain circumstances.

We discuss the two relevant prongs—and the third, irrelevant one—in turn. But first, we address four principles that, while Integra ignores them, *see* Resp. at 37-46, flow directly from the language of the FDA exemption, which allows a drug innovator to "use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information" to the FDA.

Principle 1: The relevant use is the use of the invention, not the information, and multiple purposes are permissible. When the statute prescribes that the invention may be "used . . . solely for [the] *uses*" specified, that means that the *invention* may not be put to other uses. It does not mean that the *information* generated by the accused research may not have additional uses—beyond submission to the FDA—nor that the user may not have additional purposes in generating the information. *See* U.S. Br. at 20 n.5. If an experiment is likely to be of interest to the FDA, it does not lose its immunity, for example, just because it might *also* advance the basic understanding of how the disease works. *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107-08 (D. Mass. 1998).

Principle 2: The standard is purely objective. The question whether an experiment is "reasonably related" to the FDA's regulatory function is an objective inquiry, focused on whether a reasonable researcher aware of the facts would consider the FDA a likely audience for the information generated. *See* Resp. at 29. The statutory standard is not whether the alleged infringer "reasonably believed" the information was FDA-bound, which would

entail both a subjective and an objective element. Evidence of subjective intent is irrelevant to the inquiry. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1030 (Fed. Cir. 1997); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1279 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993). Merck cannot defend on the ground that it believed the information was relevant to the FDA, if that belief was unreasonable. Conversely, Integra cannot challenge an objectively reasonable purpose, as it does at length, by trying to create an issue of fact as to whether Merck (or Scripps) subjectively harbored a different purpose. *See* Resp. at 34-36.

Principle 3: Every use is individually assessed. Because the focus is on the "use [of the] . . . invention," each use is individually measured against the standard. In this case the "use" in question is a series of experiments. As Merck argued vehemently, the JMOL ruling cannot be sustained as to any experiment that falls within the safe harbor.[2] *See* Pet. Br. at 22-23. Conversely, Integra cannot credibly insist upon deference to the jury verdict—as if the jury had "concluded that Merck failed to carry its burden of proving that [all] *the infringing experiments* were protected by the FDA Exemption," Resp. at 2 (emphasis added)—when the District Court erroneously directed the jury that it could find "all of the accused activities" lost the benefit of the FDA exemption so long as one experiment fell outside the safe harbor. J.A. 62.

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[2] Integra acknowledges that Merck objected to the contrary direction in the verdict sheet and even moved for a new trial on the basis of the error. Resp. at 17 n.9. As the Court of Appeals understood, Merck is entitled to insist on application of the correct legal standard on appeal. *See City of St. Louis v. Praprotnik*, 485 U.S. 112, 120 (1988); Transcript of Oral Argument at 10.

Principle 4: Deference to drug innovator. While Integra correctly points out that Congress "eschewed a bright line test," Resp. at 29, it is equally plain that the "reasonable relationship test" is a deferential test purposely chosen to limit any gray zone. *See* U.S. Br. at 20 (pointing out that Congress rejected a formulation limited to situations where the use was "directly related"); Genentech Br. at 19-21 (describing other contexts where "reasonably related" evokes an "arbitrary or capricious" standard). Any less protection would scuttle Congress' goal to speed promising therapies to market as soon after patent expiration as possible. If a researcher generating data about a promising therapy cannot be sure *ex ante* whether the next experiment he is poised to perform will subject him to treble damages at the whim of an unpredictable jury, he will desist. So courts must be especially vigilant to scrutinize claimed material issues of fact lest pseudoscience and hired "experts" swallow all the benefits of the immunity. *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002).

This cautionary note applies with heightened force here. Both sides agree that, for the period in question (or at least for most of it), it was perfectly permissible for Merck and Scripps to conduct research that was FDA-directed. *See infra* at 9-10. The central dispute is over whether particular experiments were on subjects reasonably viewed as relevant to the FDA. A standard that grants juries wide latitude to second-guess scientists as to what would be germane to the FDA would be at war with FDA's policy of encouraging researchers both "to exercise considerable discretion" as to what information to generate and to be expansive in their preclinical testing and in their presentations to the FDA. 21 C.F.R. § 312.22(d); *see* U.S. Br. at 21-23. Only under a deferential standard can drug innovators and the FDA hope to avoid or minimize future Thalidomide or Vioxx debacles.

C. The Accused Experiments Were Conducted When It Was Reasonable To Believe Merck Had A Commercially Viable Drug.

Turning to the temporal inquiry, no one disputes this much: There must be some point along the trajectory of drug development beyond which it would be unreasonable for a jury to reject the FDA exemption (assuming that the experiments in question are directed at FDA-relevant subjects, under the second prong). The facts of this case present the legal options starkly: Does that point arrive, as Merck argues, when a drug innovator gathers enough data from which it is reasonable to conclude it has a commercially viable drug candidate—which is to say that the research has identified a known structure that could cure a specific disease through a known mechanism? *See also* U.S. Br. at 16-17. Or is the trigger delayed until some later point in the arc, such as the moment at which the innovator has optimized the drug candidate, has fully documented its activity, knows the precise structure of the compound it wants to bring to market, and has made the business decision to proceed with expensive toxicology studies?

There is no dispute that Merck satisfies the first legal option. Integra concedes as much when it observes that: (1) by "April 1994 . . . Dr. Cheresh demonstrated that blocking the $\alpha_v\beta_3$ receptor would inhibit angiogenesis in tumors, depriving them of the blood supply they need to grow," Resp. at 12; (2) "[t]his discovery showed that . . . RGD peptides . . . could be used as a drug therapy that inhibits the growth of solid tumors," *id.*; and (3) Integra appreciated then that "Scripps' work had passed beyond the basic research stage and had advanced to the point where commercial drug possibilities were being explored," *id.* at 14. All agree: by the time Scripps performed the first accused experiment, in August, 1994, "people at Merck . . .

were interested in using an RGD peptide as a cancer drug." *Id.* (citations omitted).

While admitting that it was reasonable for Merck to have its eye on commercial development—and, therefore, on the FDA—throughout the period in question, Integra waffles as to whether this satisfied the temporal prong. Integra seems elsewhere to suggest that the critical juncture may not be reached until the drug developer definitively elects to seek FDA approval "of a specific compound," *id.* at 34, arguing that for a portion of the period in question Scripps was "'really searching for an *ideal* drug candidate,'" *id.* at 35 (citation omitted; emphasis added). Likewise, Integra asserts that "[t]he development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board approved development of [the specific] RGD compound EMD-8," *id.* at 34, which was the point at which Merck formally decided to commit enormous financial resources to bring its best compound to clinical trials.

Either way, of course, the next two years of accused experiments (the 95 experiments performed from November, 1996 to November, 1998) were within the safe harbor period, and JMOL should be granted at least as to FDA-relevant experiments in that period. The only question remaining for this Court to decide is how much further back the period of indisputable immunity extends, a question on which Integra offers no clear answer.

Two of Integra's amici are more explicit, arguing that even after an innovator has found that a specific structure has a therapeutic effect through a known mechanism, the innovator may not conduct experiments directed at "the characterization of those compounds identified, and optimization of identified compounds." Vaccinex Br. at 17; *see* Benitec Br. at 14-16. These amici reason that the FDA exemption offers no protection (at least not as a matter of

law) if "it cannot be known at the time [of the use] whether any information will ever be submitted to the FDA." Vaccinex Br. at 16.

This proposed legal standard ignores the uniform reality of what a drug developer must do en route to the FDA. No drug innovator ever commits the extraordinary resources necessary to generate toxicology data for an IND application without conducting preliminary rounds of testing—almost all of which will be submitted to the FDA, if the IND application does proceed—to justify the expense; that is what "characterizing" is. *See* Lilly Br. at 2-3. No drug company ever proceeds to clinical trials with a promising compound without first testing whether close analogs that operate through exactly the same mechanism might be safer or more effective; that is what "optimizing" or "drug design" is. *See* Lilly Br. at 6-7; U.S. Br. at 24 n.8; AIPLA Br. at 12-15; NYIPLA Br. at 13-14; J.A. 236, 416-17. That was what Merck was doing with the small portion of the Scripps research that Integra, quoting Dr. Cheresh, describes as "searching for an ideal drug candidate." Resp. at 35. As Dr. Cheresh testified in the next sentence: "Our goal was, *as we were embarking towards* developing a clinical entity for *clinical trials* . . . to identify the most effective, specific, and safest compound." Tr. 1092 (emphasis added). To conclude that this phase of preclinical research is unprotected is tantamount to abolishing the FDA exemption for the IND stage, because no reasonable drug developer will hurtle forward to clinical trials without exploring the possibility that a tweak will make the drug safer or more effective. *See* U.S. Br. at 18-19.

D. The Scripps Experiments Were Relevant To An IND Application.

While Integra's position on the temporal prong is vague, its challenge to the substantive prong is crystal clear. The

keystone of Integra's position before this Court—as it was before the Court of Appeals and the jury—is this erroneous statement of law: "in terms of data actually submitted to the FDA in an IND, only safety-related data are relevant to the decision to [permit] . . . clinical testing" to proceed. Resp. at 6; *see id.* at 5, 24. Indeed, Integra argues that the FDA is generally prohibited from considering anything else at the IND stage. *See id.* at 4. Only by positing that safety, alone, is of concern can Integra argue that Scripps was not qualified to undertake any IND-relevant preclinical studies for lack of GLP certification. *See id.* at 37-38. And only based on that premise can Integra ignore the division of labor to which Merck and Scripps agreed, and assert that Scripps did not "contribute[] anything to the generation of information above and beyond what Merck was preparing to do on its own." *Id.* at 36. The legal premise and each of its corollaries are incorrect as a matter of law.

Beyond these legal fallacies, Integra's only other challenge to this prong revolves around trying to demonstrate that Merck and Scripps continued to have interests in the collaborative research beyond FDA approval and that a fraction of the experiments were directed at comparing Merck's lead candidate to other possible analogs. These challenges also fail as a matter of law.

1. The FDA considers more than safety data in assessing an IND application, and this non-safety data need not satisfy GLP.

Integra's main theme boils down to this proposition: It is objectively unreasonable for a researcher proposing to administer a drug to humans to develop and submit to the FDA evidence that the drug could be useful in treating a disease (efficacy), or information about how the drug works (mechanism of action), how the drug circulates in the body (pharmacokinetics), or what doses or modes of

administration might be necessary (pharmacology). Resp. at 37-46.

As both Merck and the Government have demonstrated at length, numerous regulations and FDA advisories confirm that Integra's expert misstated the law: *See* Pet. Br. at 30, 46-48; U.S. Br. at 10-11, 25-26. Integra protests that the "government's arguments" are "missing . . . an appreciation" for what the FDA cares about in "the IND application process," Resp. at 45, seemingly without appreciating that "the government" in this case *is the FDA* (among other agencies). When the FDA advises this Court that FDA regulations and FDA advisories are clear, the least that can be said is that it must be reasonable, as a matter of law, for a drug innovator to interpret the FDA's regulations as the FDA does: that the IND application embraces the various other topics—efficacy, mechanism of action, pharmacology, and pharmacokinetics—that the Scripps scientists were indisputably studying.[3]

Equally incorrect as a matter of law is Integra's corollary, that Scripps "was not institutionally competent to

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[3] Integra never presented any witness to dispute the testimony from at least nine Merck witnesses that the accused experiments were reasonably related to these topics. *See* Pet. Br. at 12-13 (collecting citations to testimony by Cheresh, Friedlander, and Storgard); *see also* J.A. 334-35 (Bynum); J.A. 398-407 (Houston); J.A. 414-20 (Armitage); Tr. 2782-83 (Grimm); Tr. 1563-64 (Goodman); Tr. 2358-59 (Luckenbach). It cannot defeat JMOL now by alleging a single unrelated flaw in the testimony of four of those witnesses, Resp. at 46-47, and arguing that "the District Court was therefore required to ignore all of this testimony." *Id.* at 47. As Integra acknowledges, it is inappropriate to deny JMOL "when the evidence favoring the movant is so one-sided that, *absent adequate evidentiary response by the non-movant, it could not be disbelieved by a reasonable jury*." *Id.* (quoting 9 J. MOORE ET AL., MOORE'S FEDERAL PRACTICE ¶ 50.05[2] (3d ed. 2004)) (emphasis added).

meet FDA requirements," because only information generated by laboratories that satisfy GLP standards is permissible. *Id.* at 1; *see id.* at 37. As the Government confirms (again, speaking for the FDA), the FDA's regulations require GLP compliance for the generation of *safety* data, not for information on any of the other IND-relevant topics. U.S. Br. at 26 n.9. "[E]xploratory studies carried out to determine whether a test article has any potential utility" or on any topic unrelated to safety—exactly the sorts of tests Scripps was conducting—are not subject to the GLP requirements. 21 C.F.R. § 58.3(d); *see id.* § 312.23(a)(8)(iii). Integra could not create a genuine issue of fact on these questions by recruiting a witness to disagree with these clear statements of law. *See* Resp. at 37-39.

2. The experiments did not shed the protection of the FDA safe harbor just because Scripps and Merck were simultaneously continuing basic research and studying other candidates.

Integra does not dispute that the 1995 agreement—drafted and signed long before anyone had suggested that Scripps was infringing its patents—called upon Scripps to conduct the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials," J.A. 90; *see* Tr. 2196-97, 2357-60, 2396-401, with a view to beginning clinical trials within three years, J.A. 86, 93. But Integra tries to lift the protection of the FDA safe harbor by observing that the same agreement *also* funded Scripps to engage in other endeavors: Basic research and a continued effort to ascertain whether some analogs would achieve EMD-6's results more safely or effectively. As a matter of law, neither purpose can nullify the FDA exemption's protection.

Basic research. Integra is correct about this much: The 1995 agreement confirms that neither Dr. Cheresh nor Merck lost interest in basic research to cure diseases once they discovered the therapeutic promise of EMD-6 as a cancer cure. In addition to developing information for the FDA, "[t]he Merck-funded research was also designed generally to strengthen the 'scientific foundation' of the basic approach of blocking the $\alpha_v\beta_3$ receptor to inhibit angiogenesis in tumors." Resp. at 13 (citation omitted); *see id.* at 36.

Obviously, to the extent that Merck funded Scripps to conduct experiments other than the accused experiments, those activities are irrelevant. So, too, as we have seen, is any motive Merck or Scripps may have harbored as it was conducting the accused experiments, beyond the motive of generating data for the FDA. *See supra* at 6-7 (Principles 1 and 2). If, as we have demonstrated, the accused experiments did generate information of the sort that is relevant to the FDA, the fact that some of them *also* advanced understanding of the disease does not defeat the safe harbor's protection. In fact, virtually any effort to refine an understanding on the (IND-relevant) topic, mechanism of action, will "strengthen the 'scientific foundation' of the basic approach." *See* Tr. 1128; *see also* Tr. 1853-55.

Comparative testing. The 1995 agreement confirms also that Merck—like any reasonable drug innovator—was not prepared, at first, to bet the proverbial farm on EMD-6, and forego research on possible analogs on the chance that the lead candidate might fail or other variations might be better or safer cures for cancer. *See supra* at 10-11 (discussing optimizing candidates). With Merck's support, Dr. Cheresh explored a few possible "mimetics," compounds that were structurally similar to RGD peptides and therefore might have similar, perhaps superior, effects in animals. Tr. 456-7. These mimetics were not themselves RGD peptides, and did not, therefore, infringe Integra's patents. Tr. 490, 1546-7, 2479-80.

Integra's sole theory in this regard is that the testing of these mimetics infringed its patents, because Scripps used EMD-6 or EMD-8 as "positive controls," Resp. at 35, alongside the mimetics in some chick CAM assays to see which worked better and with fewer side effects. Tr. 1092-95. This theory fails for three reasons. First, if a particular sort of experiment generates information relevant to the FDA, so, too, does a repetition of the experiment. That the experiment also generates data about a potential competing candidate does not convert a relevant use into an irrelevancy. Second, as the discussion above on drug optimization demonstrates, comparisons of a leading drug candidate to *other* close analogs are reasonably related to the FDA approval process. *See supra* at 11. As the Government confirms, in balancing risks against benefits, it is quite relevant to the FDA whether the drug sponsor is moving into clinical trials with the candidate that is both safest and most effective. *See* U.S. Br. at 19; PhRMA Br. at 8; J.A. 236, 414-20; Tr. 1091-92. Third, even if the sponsor might opt not to present all the comparisons to the FDA, the important (and desirable) exercise of optimizing the drug candidate is still "reasonably related to the development" of the necessary information even if not to its "submission." AIPLA Br. at 15-17; J.A. 414-20.

In any event, even if the theory were valid, it would not apply to the vast majority of the experiments before the Court. While Integra emphasizes the provision of the 1995 agreement under which Merck reserved the right to send Scripps up to 100 competing drug candidates to study, Resp. at 35, the relevant focus of the statute is the challenged "use," not the inchoate plan. In point of fact, over the course of the four years at issue here, Scripps tested only 15 to 20 such mimetics, J.A. 319, and Scripps performed no comparative experiments with mimetics after May, 1997, T. Ex. 698. Moreover, of the 180 experiments at issue here,

only 19 (or 11%) involved mimetics. *See id.* So, even accepting Integra's theory, JMOL would have to be granted as to the rest of the experiments and the remainder of the timeframe.

E. Integra Has Never Alleged That Merck Lost Protection Because It Used The Inventions As Research Tools Rather Than As Objects Of Study.

Nowhere in its brief, or in any argument in the courts below, has Integra referred to the possible third prong addressed by numerous amici: that the accused experiments lost the protection of the FDA exemption *because* Scripps used the inventions as research tools rather than as objects of study. The closest Integra comes is to suggest, in its statement of facts only, that the patented compounds and uses *can be* "useful as research tools for biomedical research" and to suggest one "good example" of such a use. Resp. at 11; *see also id.* at 19 n.10 (same). But that is not the same as arguing that Merck in fact used the compounds as research tools, much less that such a use would fall categorically outside the safe harbor even if the experiments were otherwise protected. Had Integra ever pressed that theory, it would not have prevailed because the experiments in question used EMD-6 and its analogs as the objects of study and in ways that lie at the very heart of the FDA exemption. *See* U.S. Br. at 28 n.11; NYIPLI Br. at 21-25.

Thus, the complex question whether research tools should ever be excluded from the ambit of the FDA exemption, and if so under what circumstances, has no bearing on the outcome of this case. Whereas the Court of Appeals invoked the impact on research tools as a justification for excluding preclinical research from the statutory exemptions, there is no dispute among the parties as to that question of statutory construction. This Court has

neither the occasion nor the record on which to resolve the issue today.[4]

II. THERE IS NO BAR TO REVERSING THE COURT BELOW.

Integra urges this Court not to cure the Court of Appeals' error, arguing that (a) Merck did not challenge the sufficiency of the evidence on appeal; and (b) Merck did not preserve its primary argument in its certiorari petition. Both positions are incorrect.

The JMOL briefing in the Court of Appeals. Merck did challenge the sufficiency of the evidence on appeal, just as it did at the trial level. Merck's brief before the Court of Appeals featured this heading: "No Substantial Evidence Exists to Conclude that Scripps's Experiments Did Not Reasonably Relate to the Development of Information for the FDA's Approval of an IND for EMD 12[]." Merck CA Br. at 50. Within this section, Merck argued, just as it does here, that "Merck established that all of the data from the accused experiments was *itself* germane to the IND for EMD 12[] and was likely to be submitted to the FDA for that

[4] One amicus brief suggests that the Court of Appeals actually held that Merck used the inventions here as research tools—a proposition Integra has not advanced—and that Merck is precluded from challenging that determination now. *See* Invitrogen Br. at 18-19. The Court of Appeals' discussion of the FDA exemption did not even suggest that Scripps was using the inventions as research tools, much less revolve around any such assumption. P.A. 13a-14a. Only later, in discussing the appropriate measure of damages, did the majority suggest that the "research tool" label could be apt, and even there the majority noted that it would have reached the same conclusion "[r]egardless of whether one considers the RGD peptides to assume the label of a 'research tool.'" P.A. 22a n.4. The reference to research tools in the context of damages was not a "holding." Invitrogen Br. at 20.

purpose." *Id.* (emphasis added). After summarizing the evidence, the brief concluded, "*In view of the foregoing, no reasonable jury could have found that the accused experiments were not exempt under § 271(e)(1).*" *Id.* at 51 (emphasis added). On reply, Merck consumed six pages parsing the evidence Integra adduced in support of the verdict, Merck CA Rep. at 7-13, and repeated the same conclusion, *id.* at 13.

In sifting through the evidence, Merck embraced the so-called "*Intermedics* test" that formed the basis of the jury instruction. Merck CA Br. at 46-47; Merck CA Rep. at 3; *see Intermedics*, 775 F. Supp. at 1280. To be sure, in interpreting the *Intermedics* test, Merck argued, at points, that "Congress must have intended the phrase 'uses reasonably related to the development and submission of information' to the FDA to encompass drug development research that serves as a rational predicate to generating information for submission to the FDA, *including any tests to determine whether to proceed with a drug candidate*." Pet. Br. at 45 (emphasis added). Even if Integra were correct that this was an "aggressive legal theory," Resp. at 20—rather than, as the italicized language suggests, simply another way of restating the legal standard that was already used in the case—it would not change the reality that Merck *also* argued that the evidence was insufficient on any theory.

The Certiorari Petition. Contrary to Integra's rendering, this case is not about "[w]hether the District Court properly instructed the jury" about the legal standard. *Id.* at i. As Integra points out there is no dispute about the basic legal standard captured in the jury instruction (although future trial courts will undoubtedly refine the instruction in light of this Court's guidance). *Id.* at 31. This is an appeal from a denial of JMOL. In that context, Merck's certiorari petition presented the following question for review: "Did the

Federal Circuit err in concluding that [the FDA] safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, *where the research will be presented to the FDA . . .?*" Pet'n at i (emphasis added).

This question is virtually identical to the question posed in Merck's opening brief. It is a mystery, then, why Integra claims that "Merck seemingly reasserted its 'rational predicate' argument," Resp. at 20; *see id.* at 21, 22, and presented "this Court with [an] argument that basic drug research activities are covered by the safe harbor," *id.* at 27-28; *see id.* at 2. Even accepting the premise that the "rational predicate" concept represented a more aggressive position, the phrase appears nowhere in the petition. When Integra characterized Merck's certiorari petition that way, *see* Cert. Opp. at 2, Merck corrected the misimpression, insisting that its proposed standard covers "studies [that] are well down the long road of pioneer drug research," Pet'n Rep. at 2.

In short, Merck has not "backpedaled" and "disclaimed" the position it took in seeking certiorari, Resp. at 21, but has maintained since the summary judgment phase that no reasonable juror could reject the FDA exemption under the prevailing legal standard.

CONCLUSION

The ruling of the Court of Appeals should be reversed with directions to enter judgment for Merck.

Respectfully submitted,

Donald R. Dunner
Thomas H. Jenkins
FINNEGAN, HENDERSON,
FARABOW, GARRETT &
DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, DC 20001
(202) 408-4000

E. Joshua Rosenkranz
Counsel of Record
M. Patricia Thayer
James N. Czaban
Gina M. Parlovecchio
Nishita Doshi
HELLER EHRMAN LLP
Times Square Tower
7 Times Square
New York, NY 10036
(212) 832-8300

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